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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,291	09/18/2006	Roberto Tonelli	BUG5-38919	4354

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
10/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/554,291	TONELLI ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7-13* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8,9 and 13* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/2010 has been entered.

Election/Restrictions

Claims 10-12 and "amino acid carrier" species other than "PKKKRKV" remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species respectively, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/23/08.

Priority

Applicant submission of a certified translation of the foreign priority papers is acknowledged.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 8, 9, and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sun et al [Peptides Vol.23:1557-1565, 2002, cited by applicant] and Cutrona et al [Nature Biotechnology Vol 18:300-303, 2000, cited by applicants].

The claimed invention is as set forth in the rejected claims.

Sun et al have taught the use of PNA antisense oligomers[12mers and 15mers] with carrier peptides attached to the 3' end of the oligomers where the PNA oligomers target and inhibit N-myc. It has been taught that carrier peptides are beneficial for cell penetration of PNA oligomers. It has also been taught that inhibition of expression of N-myc is desirable to inhibit N-myc for tumor growth inhibition. Sun et al do not teach antigene sequences targeting N-Myc and also do not teach the use of a carrier peptide PKKKRKV.

However Cutrona et al have taught the use of PNA antigene oligomers[sense] for inhibiting a desired gene. The PNA antigene oligomers of Cutrona et al were 17mers and also utilized the carrier peptide PKKKRKV. It has been taught that the use of this carrier peptide facilitates the entry of PNA oligomers into cells. Cutrona also teach the use of PNA oligomers for the inhibition of a target gene to inhibit tumor growth.

The art taken as a whole shows that the instant invention is obvious. The art has shown that it is desirable to inhibit N-myc to inhibit tumor cell growth. The prior art has shown a PNA antisense oligomer inhibiting N-myc expression in cells and has also shown the use of antigen [sense] PNA oligomers for use in inhibiting a desired gene. The prior art has shown that carrier peptide are beneficial for use with PNA oligomers to facilitate there delivery into cells. The prior art has specifically taught that the peptide

carrier PKKKRKV is a peptide carrier that facilitates PNA oligomer entry into cells. The prior art has shown PNA oligomers of various sizes within the recited size range recited in the claims and further it is noted that the size range recited is within the art recognized sizes for the use of antisense applications for target specificity and efficient delivery. One would be motivated to make either antisense or sense PNA oligomers targeting N-myc since the art clearly shows that antisense oligomers targeting N-myc function to inhibit N-myc and since the art has shown that antigen sequences[sense] can also be used to inhibit a desired gene target. One would be motivated to utilize peptide carriers since the art has taught that such carriers are required for effective delivery into cells. One would be motivated to inhibit N-myc since the art has indicated that inhibition of N-myc can inhibit tumor growth.

The invention as a whole would therefore have been prima facie obvious to one in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 8/18/2010 have been fully considered but they are not persuasive.

First the declaration of Roberto Tonelli is acknowledged. The declaration shows that other antigene PNA molecules have been demonstrated to inhibit N-myc expression in specific cells. The examiners position set forth in the previous Official Action was that the superior inhibition of antigene compared to antisense was not

sufficiently described in the specification as filed to demonstrate an unexpected property of the scope claimed compounds. Although applicant has demonstrated more PNAs that inhibit N-myc expression, which property of the claimed compounds was not questions by the examiner, it is unclear how the demonstration of more PNA antigene compounds provides evidence of unexpected properties without a comparison with ant more antisense compounds where an evaluation of unexpected properties could be established. If applicant has would like to further explain the declaration to the examiner he would indeed be willing to discuss the declaration.

Now to the arguments. Applicant has argued several points in arguing the invention as nonobvious over the prior art.

Applicant asserts that the research purpose of Sun et al has to develop "a different and more tumor specific approach via the addition of analogs of hypothalamic peptide somatistatin which allows delivery to cells) especially tumor cells) that express somatostatin receptors. Applicant points out that Sun et al use antisense PNA constructs targeting N-myc. This has been recognized in the rejection and arguments of the examiner of record. Applicant notes that N-myc inhibition was observed in neuroblastoma IMR32 cells but not in GH3 cells. The examiner notes that Sun et al have taught that IMR32 cells, which amplify N-myc and expressSSTR2 were considered ideal for inhibition with their constructs (see page 1560-1561 section 3.4). At page 1561, section 3.6 it was taught that the other cell lines, including GH3 cells showed insignificant inhibition "as expected".

Applicant then provides the following in regard to the Cutrona reference. Applicant asserts that the purpose of this study was to explore conditions that would make antigene PNAs effective in cells in vitro. The conjugate used by Cutrona et al was the same recited peptide of the invention PKKKRKV. Applicant then asserts that this was done in Burkitts lymphoma cells where c-myc was overexpressed. Applicant asserts that the primary focus of Cutrona were focused on PNA delivery. None of the above in regard to Cutrona is contested.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the cited prior art is different with respect to the purpose of the pending application where applicant asserts that this purpose is for treating pathologies caused by N-myc over expression etc. The examiner notes that the claimed invention is drawn to a compound where its intended use has no patentable weight in considering the obviousness of the compound.

Applicant argues that Sun et al refers to antisense inhibition of N-myc while the claimed invention is drawn to antigene compounds targeting N-myc. The examiner notes that Sun et al have also taught that it was known in the art to also use PNAs a antigene compounds, see page 1564 and see the examiner argument set forth in the final rejection mailed2/10/2010 and reproduced below. The difference in mechanism

does not appear to be a major consideration here since the prior art has taught that both antisense and antigene techniques can be used to inhibit the expression of a target gene where the cited prior art does provide an example of each technique with related genes.

Applicant then argues that the cells used by Cutrona et al are not the same type of cells used by applicant. It is noted, however that Sun et al have taught neuroblastoma cells with n-myc amplification where inhibition of N-myc was successful with antisense PNA targeting N-myc.

What applicant response fails to show is what the cited references taken together teach. The references have established that inhibition of N-myc in cells that overexpress n-myc with antisense PNAs was successful and that the prior art also teaches that PNAs can be used as antigene inhibitor where the result of either technique is the inhibition of expression of a target gene. The prior art has provided motivation to target n-Myc based on its association with neuroblastoma. The prior art has taught that PNA compounds can be used to inhibit a target gene were the prior art has provided advantages of using PNA compounds. The prior art has also taught that PNA delivery can be enhanced via linking the PNA to a cell membrane permeating moiety. The issue at hand appears to be that applicant believes that utilizing a sense PNA in inhibiting n-myc defines over the prior art since applicant may have shown that PNA antigene compounds may work better that antisense PNAs. This, however do not carry sufficient weight in the obviousness of making the compound. One in the art would have known at the time of the invention that a sense PNA targeting n-myc could be utilized in assays

such as those described by Cutrona et al. this is because, yes Cutrona was interested in determining enhanced cellular delivery of PNA compounds. One in the art would have recognized fro example, that a more appropriate cell line to test a N-myc antigene PNA would be cells such as those taught y Sun et al, for example. Sun et al did teach that PNAs could be used as either antisense or antigene compounds.

Examiner arguments mailed 2/19/2010 reproduced.

Applicant's arguments filed 11/09/09 have been fully considered but they are not persuasive. Applicant asserts that the sense compounds of their invention have been shown to have improved down regulation as compared to antisense compounds. This in not agreed with for the following reason. The instant specification shows that one particular sense compound inhibited better than one particular antisense compound. These results are not commensurate in scope with what is claimed. The invention is drawn to any sense compound targeting n-myc where it is not clear that applicants results necessarily translate to the genus of compounds claims. Applicant provides an assessment of the differences of the targets of the prior art and that which is the subject of the instant invention. The prior art teaches inhibition of n-myc via antisense compounds and c-myc via sense compounds (both PNA). It is noted that applicants discussion of the differences of the different targets are not on point for how the references are applied. Sun et al have shown inhibition of n-myc via antisense PNA and have provided motivation to inhibit n-myc. Applicant is directed to page 1557 were Sun et al assert that PNAs provide perhaps the most promising antisense compounds..

On page 1558, first column it has been taught that n-myc, c-myc and l-myc are all related and all are important targets for inhibition. It is also noted by Sun et al that antigene methods have been employed in inhibiting c-myc. At page 1564 it has been taught, in general terms, that PNAs can be used to inhibit both translation and transcription. Sun et al, while not specifically employing an antigene method of inhibiting n-myc, clearly indication that PNAs can be used in either method of inhibiting a desired gene target. Now to Cutrona et al who have used antigene methods to inhibit c-myc. This reference should be viewed as explained in the rejection. The teachings of Cutrona et al. For example Cutrona et al assert that their study was intended to explore the conditions that would make anti-gene PNAs effective in intact cells (see page 300, for example). C-myc was chosen to show the general applicability of antigene PNA inhibition. The art taken as a whole doe show that use of PNA as antigene inhibitors was known in the art at the time of the instant invention. Furthermore it was known to inhibitc-myc via antisense and sense methods. It was known in the art to inhibit n-myc via PNA antisense compounds. The prior art cited in the rejections is related art as evidenced by the discussion of Sun et al in regard to l-myc, c-myc and n-myc. One in the art would surely have looked to the teaching of the cited art and known that one could employ either sense or antisense mediated inhibition of c-myc, l-myc or n-myc.

Claim 7 is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

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